REMARKS

Claims 1 and 3-46 are in the application. Claims 15 -17 have been amended. The amendments to the tradenames are supported by the US/EP and JP pharmacopeias for these polymeric carriers. Copies of the manufacturer's data sheets indicating such as enclosed herewith.

The Examiner comments on page 6 1rst¶ of the Office action that 'applicant's withdrawal of claims 13, 39, and 46 is improper". Clarification is requested as Applicants have never held claim 13 withdrawn from consideration. Claims 39 and 41 are product by process claims and have now been indicated as "original" as they were contained in the PCT filing and national stage entry.

Rejection under 35 USC §112

Claims 1, 3, 6, 8-13 15-22, 24, 39 and 46 are rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants respectfully traverse this rejection.

Claim 1 recites the term "homogeneously" which the Examiner deems to be a 'term of degree', and that the specification provides no indication how, what, when or where the integration of a polymeric carrier by an amorphous form of a pharmaceutically acceptable active agent might be measured and deemed homogenous or not homogenous.

The skilled artisan would readily be able to determine whether an active agent was homogenously dispersed within a formulation. This is not a 'new' activity for a pharmaceutical dosage forms. There is nothing unusual about this term, nor does it vary from its common dictionary meaning.

In the citation below, retrieved from dictionary.reference.com (shown below), no.2 "Uniform in structure or composition throughout" is clearly the intended meaning.

"ho·mo·ge·ne·ous HEAR (hō'mə-jē'nē-əs, -jēn'yəs)
adj.

1. Of the same or similar nature or kind: *"a tight-knit, homogeneous society" (James Fallows).*
2. Uniform in structure or composition throughout.
3. *Mathematics* Consisting of terms of the same degree or elements of the same dimension"

It is imperative in pharmaceutical development of a dosage form that one know how much of a drug is in a given weight of powder, etc. in order to accurately measure the amounts for a pressed tablet or capsule fill, etc. If the drug is not dispersed in the powder, or in this instance within the fiber in a homogenous or "uniform" manner, there would be great difficulty in using this technology for its intended purpose, e.g. administration as a dosage form.

The Examiner similarly rejects the term "stable" also present in claim 1. For similar reasons, the skilled artisan is well aware of how to measure stability of a drug. For the purposes of amorphous forms of a drug keeping the drug in this amorphic form is the desired end product. It is not desirable for the drug to return to a crystalline state. This is readily determinable by the skilled artisan. In fact, a number of 'negative' findings of a drug returning to its crystalline state are demonstrated in Applicants working examples in the specification. These reversions appear in non-amorphic polymeric carriers. Consequently, while this is something the skilled artisan would already be aware of, the actual demonstration of such is believed to provide any additional 'training' to the artisan should this have been necessary.

The Examiner also rejects the claims for the term 'drug substance' and lacking antecedent basis. Claims 16 and 17 have been amended to recite "pharmaceutically acceptable active agent" as present in claim 1 from which they depend.

Claim 9 and 15 are stated as reciting the limitations Triton X-200 and numerous Eudragit polymers, which are all trademarked products. Claims 9 and 15 has been amended to recite the appropriate surfactant name and the various compendium names for these polymers.

In view of these amendments and remarks, reconsideration and withdrawal of the rejection to the claims under 35 USC §112, second paragraph is respectfully requested.

Rejection under 35 USC §112

Claims 1, 3, 6, 8-13 15-22, 24, 39 and 46 are rejected under 35 USC §112, first paragraph as being indefinite for failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The Examiner rejected claim 1 and those dependent thereon on the basis that while the specification is enabling for making electrospun fibers with amorphic forms of an active agent, it is not enabling for making "stable" forms of these fibers with an active agent.

The specification is quite clear on how one would determine the stability of an amorphic active agent over time. For instance, on pages 15-18 of the specification general procedures for making electrospun fibers, determining drug content, drug solubility and drug amorphicity and its stability over time (see in particular pages 16-17, an excerpt of which is shown below:

> The amorphous nature of the drug in the formulation and its stability on ageing at 25^0C and zero humidity, was determined by XRPD. The instrument is a Bruker D8 AXS Diffractometer. Approximately 30 mg of sample is gently flattened on a silicon sample holder and scanned at from 2-35 degrees two-theta, at 0.02 degrees two-theta per step and a step time of 2.5 seconds. The sample is rotated at 25 rpm to reduce preferred orientation. Generator power is set at 40mA and 40 kV.
>
> The amorphous nature of the drug was also confirmed by MDSC (TA instruments, New Castle, DE). The samples in hermetically sealed aluminium pans were heated from 0 to 200, or to 250°C at 2°C/min at a modulation frequency of ±0.159°C every 30 seconds.

Thermal analysis and XRPD are commonly used techniques and the skilled artisan would readily be able to determine if an amorphic form of an active agent crystallized out over time, thus no longer remaining in the amorphous form.

The specification, as noted above previously, also contains working examples wherein a drug formulated in an amorphous form, did crystallize out over time, thus not being a 'stable' form in the fiber. In these noted instances, a non-amorphous polymeric carrier was used.

Consequently, it is believed that not only would the skilled artisan be readily able to make these necessary determinations, the specification quite clearly teaches one how to use the invention and make such determinations as need be.

In view of these remarks, reconsideration and withdrawal of the rejection to the claims under 35 USC §112, first paragraph is respectfully requested.

Rejection under 35 USC 103

Claims 1, 3, 6, 8-13 15-22, 24, 39 and 46 are rejected under 35 USC §103 as being unpatentable over Ignatious (WO 01/54667), in view of Pendyala (WO 02/56867), Hale (WO 00/76961) and Verreck (Pharmaceutical Res. 2003). Applicants respectfully traverse this rejection.

Clarification of the rejection is requested. The rejection (shown below) includes the phrase "as evidenced by ……". It is unclear whether the Examiner is including these references which follow this term within the rejection.

> **Claims 1, 3, 6, 8-13, 15-22, 24, 39 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ignatious [WO 01/54667 (2001), see PTO-892 dated March 25, 2009], in view of Pendyala [WO 02/56867 (2002), see PTO-892], Hale [WO 00/76961 (2000), see PTO-892] and Verreck [Preparation and characterization of nanofibers containing amorphous drug dispersions generated by electrostatic spinning, Pharmaceut. Res. 20, 810-817 (2003), see IDS dated February 7, 2005], as evidenced by the Chemical Abstract Service entry for CAS 313682-08-5 [see PTO-892], Encyclopedia Britannica Online entry for Chemistry of Industrial Polymers, see [PTO-892] and Mehta [Release performance of a poorly soluble drug from a novel, Eudragit-based multi-unit erosion matrix, Int. J. Pharmaceut. 213, 7-12 (2001), see PTO-892].**

Ignatious is stated by the Examiner "teaching pharmaceutical compositions comprising an electrospun fiber of a pharmaceutically acceptable polymeric carrier integrated with a pharmaceutically acceptable active agent".

This is correct. What the Ignatious reference does not recognize is the present invention e.g. that by using the process of electrospinning, an active agent in its amorphic form can be stabilized for use in a dosage form. Ignatious teaches that not all polymers can be spun but that there are many different polymeric carriers that can be, and that one can include an active agent in these carriers. There is no suggestion that the carriers be amorphic, nor that by spinning they could stabilize an amorphic form of a drug.

The Examiner cites the Pendyala patent to address the failure of Ignatious to use the elected polymeric carrier, Eudragit L 100-55.

Pendyla discloses use of a polymer in a completely unrelated manner to that claimed herein.

> According to another embodiment the invention also provides a process for the preparation of the above said composition, which comprises
>
> i) Preparation of granules comprising drug.
>
> ii) Coating of the granules with a polymer dissolved in a mixture of organic solvents along with a plasticizer and anti-adherent.
>
> iii) Formulating the granules into tablets or capsules or dry syrup for reconstitution with suitable pharmaceutical additives.

Pendyla utilizes polymers in a normal manner for coating a granule containing the drug and then formulating the coated granules for use in an oral dosage form.

There is no disclosure in Pendyla of stabilizing an amorphous form of a compound. There is no disclosure in Pendyla that one can stabilization an amorphic form for use in delivering the active compound to a subject in need thereof as an amorphous form of the compound (as opposed to a crystalline form).

There is no teaching nor suggestion that one could in fact use the claimed process herein to produce the end result, e.g. the stabilization of solid dispersions of amorphous drugs in polymeric nanofibers.

Why would the skilled artisan even choose an amorphous morphology of an active agent to work with if the form is generally so unstable as to be useful for commercial activities and clinical work? Solid dispersions while known in the art, are often difficult to formulate and administer consistently to patients. The present invention produces a way to do so. In fact, "*the present invention provides a novel vehicle which provides a means to allow a crystalline form of a drug to be stabilized in its amorphous form, or to take an amorphous form of a drug and retain its morphology in a controlled environment, i.e. the spun fibers. This can be used as noted, as a means to increase the surface area (nanoparticle size, etc.) and to improve its dissolution rate characteristics." (page 5)*

Pendyla provides nothing to solve the deficiencies present in the Ignatious reference. Pendyla utilizes technology in a manner which is well known in the art, and does not provide the motivation to direct the skilled artisan to use the L 100-55 polymer in the manner needed with Ignatious to achieve the invention as claimed herein.
This same failure is present in the Hale patent, which likewise does nothing to solve the deficiencies present in the Ignatious reference.

Verreck et al. is a reference which published in May 2003. Applicants filed their provisional application 7 August 2002 and foreign filed their application via the PCT on 7 August 2003.

The Examiner indicates on page 2 of the Office Action that Applicants are not entitled to the benefit of their "earlier filing date under 35 USC 119(e) since applicants do not have full support for the instant claims". Applicants respectfully disagree with this determination.

There provisional application describes on page 9 the following (italics added):
Representative examples of these polymers for purposes herein include, but not limited to, poly(ethylene oxide), polyvinyl alcohol, polyvinyl acetate, polyvinyl pyrrolidone, hyaluronic acid, alginates, carragenen, cellulose derivatives such as carboxymethyl cellulose sodium, methyl cellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropylcellulose, *hydroxypropylmethyl cellulose*, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, noncrystalline cellulose, starch and its derivatives such as hydroxyethyl starch, sodium starch glycolate, chitosan and its derivatives, albumen, gelatin, collagen, *polyacrylates and its derivatives such as the Eudragit family*

of polymers available from Rohm Pharma, poly(alpha-hydroxy acids) and its copolymers such poly(caprolactone), poly(lactide-co-glycolide), poly(alpha-aminoacids) and its copolymers, poly(orthoesters), polyphosphazenes, poly(phosphoesters), and polyanhydrides, or combinations thereof.

Example 5, which specifically uses the polymer Eudragit L100-55 is presented in the application as of the August 2003 date. However, Applicants allege that the general description of amorphous polymers, e.g. *polyacrylates and its derivatives such as the Eudragit family of polymers available from Rohm Pharma*, coupled with the description of a polymer which is necessary to support the invention, e.g. an amorphous polymeric carrier would encompass the specific species of L100-55. However if the Examiner requires an affidavit under 1.132 to swear behind the Verrack reference, one will be submitted. Thus it is believed that the Verrack reference is not a suitable reference for use in this rejection.

Consequently, the Office is failing to consider the invention as a whole, and has not established a *prima facie* case as stated by the Examiner on page 24 of the Office Action.

The PTO has not satisfied their three requirements:

1) the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references.
2) the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. In other words, a hindsight analysis is not allowed. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991); and
3) the prior art reference or combination of references must teach or suggest all the limitations of the claims. *See In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art.").

As discussed above, the prior art relied upon by the Examiner would not motivate nor direct the skilled artisan to the problem, e.g. using an amorphous polymeric carrier to stabilize

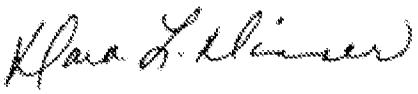
and amorphous form of a drug in an electrospun fiber. Therefore, the USPTO has failed to establish a *prima facie* case of obviousness.

In view of these remarks, reconsideration and withdrawal of the rejection to the claims under 35 USC 103 is respectfully requested.

CONCLUSION

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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